California MEDICINE
OFFICIAL JOURNAL OF THE CALIFORNIA MEDICAL ASSOCIATION

Volume 95 AUGUST 1961 Number 2

Parathyroid Tumors

Intermittent Function, a Pitfall in Diagnosis

RALPH J. VEENEMA, M.D., New York

• Seventy cases of functioning parathyroid tumors encountered at Columbia-Presbyterian Medical Center were reviewed. The clinical and chemical findings in parathyroid tumors were variable and were suggestive of intermittent function. The indirect diagnostic tests available today usually paralleled the basic serum calcium and phosphorus determinations. Urolithiasis was the most common complication observed, but the symptoms of it varied from simple colic and single calculus problem to extensive calculus disease. There were two instances of hyperparathyroid crisis or "hypercalcemic poisoning."

As UROLOGISTS are frequently faced with the problem of recurrent renal calculi and the differential diagnosis in instances of hypercalcemia and hypercalciuria, it is natural for them to have an unusual interest in the problem of functioning parathyroid tumors. A careful study of the problem of these tumors impresses one immediately with the difficulties of diagnosis.

The clinical symptoms and signs of hyperparathyroidism vary greatly and affect many systems. Although renal and skeletal symptoms are most common, many patients also have gastrointestinal and neuromuscular symptoms. In the 70 cases of functioning parathyroid tumor reviewed in this study at Columbia-Presbyterian Medical Center from 1932 through 1959, there were five patients who were initially admitted to the Neurological Institute for investigation of headache and neuromuscular weakness and were subsequently found to have hyperparathyroidism. Three patients had symptoms primarily referrable to duodenal ulcers.

In general, the symptomatology can be classed as (1) *nonspecific symptoms,* such as weakness, easy fatigability, irritability, weight loss and epigastric distress; (2) *symptoms referable to the kidneys;* (3) *symptoms referable to the skeleton,* such as bone pain, pathological fractures and deformities. The symptomatology seems to follow no apparent sequential pattern—that is, renal involvement often precedes skeletal lesions and vice versa.

It is thus evident that symptomatology cannot be entirely reliable. Direct assay of parathormone is not a clinically applicable test as yet. It would be most helpful if such a direct assay were available, but we must rely on indirect chemical tests for diagnosis. The actual mechanism of action of the parathyroid hormone is still a subject of much study, but in general it can be stated that the chemical tests that are useful today are based on the two following actions of the hormone: (1) The mobilization of calcium from the skeleton, (2) the inhibition of reabsorption of filtered phosphate by the renal tubules, or so-called phosphate diuresis.

These indirect chemical tests such as the intravenous calcium loading test,[5] 24-hour urinary cal-

From the Squier Urological Clinic, Columbia-Presbyterian Medical Center, New York 32, New York.

Guest Speaker's Address: Presented before the Third General Meeting at the 90th Annual Session of the California Medical Association, Los Angeles, April 30 to May 3, 1961.

cium determination, phosphate clearance, tubular reabsorption of phosphate[3,8] and the basic serum calcium and phosphorus determinations, are helpful, but no single test is absolutely diagnostic. The chemical diagnosis is also limited by the fact that the reliability of these tests is dependent upon normal renal function and normal serum protein. All too often the results of the more complicated tests are equivocal and borderline whenever the serum calcium and phosphorus are also equivocal and borderline. Another limiting factor in the chemical diagnostic tests is an apparent intermittent function of the parathyroid tumor.

A careful study of the cases of functioning parathyroid tumor observed at the Columbia-Presbyterian Medical Center reemphasized the variability of the chemical findings, the lack of characteristic general clinical features and the lack of characteristic urological symptoms and findings. The study also emphasized the possibility of occurrence of hyperparathyroid crisis or "hypercalcemic poisoning." A need was evident for earlier surgical exploration and more liberalized criteria for surgical exploration to avoid the potentially fatal outcome of hyperparathyroidism.

CLINICAL FEATURES

From 1932 through 1959, 70 patients with functioning parathyroid tumor were observed at the Columbia-Presbyterian Medical Center (Table 1). Adenomas predominated in this series and in two patients recurrent adenomas were found. There were three carcinomas of the parathyroid gland removed. Two of these were functioning carcinomas, and in one instance a metastatic lesion from the tumor was functioning. The three patients with carcinoma died, two, three and six years after diagnosis, despite radical neck dissection and radiotherapy. Cases of hyperplasia of the parathyroids were excluded from this study.

Female patients predominated in a ratio of three to two and the incidence was highest in the 30 to 60 year old group. The youngest patient was age 11 and the oldest 76 years.

Urolithiasis was a clinical feature in 50 of the 70 patients with functioning tumors. One of the patients with functioning carcinoma had renal calculi and one did not. The time interval from diagnosis of calculus disease to removal of parathyroid tumor was as little as two weeks and as long as 18 years. The average was 5.6 years.

There was no identifiable uniformity of clinical features that could be considered characteristic of cases in which there was a calculus problem. Multiple and bilateral calculi, as expected, were common. All calculi were opaque, but of varying degrees of opacity. Typical nephrocalcinosis was present in only ten patients and in seven patients only a single calculus was present. Staghorn calculi were present in five of the 50 patients with calculi. In general one can state that the urolithiasis varied from simple colic and single stone to extensive calculus disease. (See Table 2.)

Most of the stones were of mixed chemical makeup, but calcium phosphate was common to all the mixed stones, and five of the eight pure stones in the series were calcium phosphate. Two of the other three pure stones were calcium oxalate stones and one was made up solely of uric acid. The patient with the uric acid stone also had gout and it is questionable what relationship the parathyroid tumor played in the calculus disease.

A total of 51 urological operations were performed on 31 of the 50 patients with urolithiasis. In 19 patients with calculus disease and functioning parathyroid tumors, no urological operation was indicated. The multiplicity of operations reemphasizes the magnitude of the calculus problem frequently encountered in patients with a functioning parathyroid tumor. (See Table 3.)

TABLE 1.—*Data on Cases of Parathyroid Tumors Observed at Columbia-Presbyterian Medical Center (1932 Through 1959)*

Functioning tumors:	
Adenomas	70*
Carcinomas	2
Non-functioning tumors:	
Adenomas	6
Carcinomas	1

*Includes two recurrent adenomas.

TABLE 2.—*Clinical Features of Urolithiasis in 50 Patients with Functioning Parathyroid Tumors*

	No. Patients
Recurrent calculi	25
Bilateral calculi	29
Opaque calculi	50
Single calculus	7
Multiple calculi	33*
Nephrocalcinosis	10

*Staghorn calculi in five patients.

TABLE 3.—*Operations for Urolithiasis in 50 Patients with Functioning Parathyroid Tumors*

	No. Patients
Number of operations:	
None	19
Single	17
Multiple	14
Types of operations:	
Ureterolithotomy	20
Pyelolithotomy	10
Nephrolithotomy	8
Nephrectomy	9
Cystoscopic extraction	2
Cystolithotomy	2

After removal of the parathyroid tumor, 17 patients had no further calculi, and in one patient calcification of the kidney seemed to decrease. Results, however, were not always good. Poor results were mainly due to persistent stones, chronic urinary infection and renal insufficiency. There were nine deaths due to renal insufficiency. In these nine patients an average of 6.2 years elapsed from the time of diagnosis of renal calculi to the date of removal of the parathyroid adenoma, and the postoperative survival averaged 7.4 years.

HYPERPARATHYROID CRISIS OR "HYPERCALCEMIC POISONING"

An extremely interesting clinical entity encountered in this series of seventy functioning parathyroid tumors was hyperparathyroid crisis. There were two such cases. One patient was a 56-year-old woman who died following ureterolithotomy. She was admitted with a ureteral calculus obstructing a solitary kidney. Initial hypercalcemia was noted and parathyroid adenoma suspected, but the pressing urological problem took priority. Seven days after ureterolithotomy the patient became lethargic, which was followed by high fever, oliguria, circulatory collapse, cyanosis and coma. In spite of supportive therapy she died on the tenth postoperative day, at which time serum calcium was 19.4 mg. per 100 cc. At autopsy a parathyroid adenoma with focal necrosis was found. The cause of death was considered to be the toxicity of hypercalcemia plus bacteremia.

A second case of hyperparathyroid crisis was that of a 70-year-old white man with multiple bilateral renal calculi and preoperative serum calcium of 12.5 mg. per 100 cc. A parathyroid tumor was removed from his neck on June 25, 1952. Postoperatively the serum calcium rose, from levels of 12.5 and 14.6 preoperatively, to 17.0 and 18.0 mg. per 100 cc. postoperatively. Oliguria and renal failure developed and the patient died in what seemed to be uremia. At autopsy a 4 cm. tumor was found below the clavicle. It appears that this tumor continued to function and led to death.

The entity of hyperparathyroid crisis is fortunately rare, but its gravity is not sufficiently appreciated. James and Richards[6] reported a case of hyperparathyroid crisis which was successfully treated by doing an emergency parathyroidectomy. It is reassuring to know that emergency parathyroidectomy can be done if one is faced with this fatal problem. It is apparent that it is potentially dangerous to do a urological procedure in the presence of evidence of hyperparathyroidism. Surgical stress and immobilization seem to be sufficient to precipitate the onset of a hyperparathyroid crisis. The use of supportive therapy with steroids and the use of a chelating agent, such as EDTA would also be helpful today. An entity such as hyperparathyroid crisis further indicates that there is variation in the action of parathyroid tumors.

CHEMICAL ASPECTS OF FUNCTIONING PARATHYROID TUMORS

Two of the greatest pitfalls in the diagnosis of parathyroid tumors are that the chemical diagnostic tests depend upon normal renal function and apparent chemical indications of intermittent function of parathyroid tumors. Since variable serum calcium and phosphorus levels are rather commonly found, making these tests untrustworthy, we have also pursued other chemical diagnostic tests, as noted previously.

Our experiences with the tubular reabsorption of phosphate test done in the last two and a half years on 60 patients with calculus formation showed 35 results within normal range, 13 borderline low and 12 distinctly low. In five of the 12 with low reabsorption, parathyroid adenomas were found at operation. Parathyroid hyperplasia was present in another patient, and parathyroid cyst in yet another. The remaining five patients were not operated upon. As a rule the results of other chemical tests paralleled those of the tubular reabsorption of phosphate test.

It has sometimes been stated that a skeletal survey is unnecessary if alkaline phosphatase is within normal range. This is not necessarily so. In eight of 70 patients with functioning parathyroid tumors, varying degrees of skeletal changes in demineralization were observed, which aided in the diagnosis of hyperparathyroidism, although serum alkaline phosphatase values showed no abnormality. Three of these patients had typical ostitis fibrous cystica, and in one of these three the bone changes were so extensive that "osteoblastic exhaustion" was the explanation given for the repeatedly normal serum alkaline phosphatase.

Repeated determinations of serum calcium and serum phosphorus levels remain the most practical tests. In the present series of 70 patients with functioning parathyroid tumors the highest serum calcium levels in individual patients (Chart 1) were from 20.3 mg. per 100 cc. down to 10.6 mg. per 100 cc. In three of the patients the serum calcium levels never rose above 11.2 mg. per 100 cc. In one patient the serum calcium value varied from 9.8 mg. to 11.0 mg. per 100 cc. within a one-month period. In the same period the patient had serum phosphorus varying from 2.2 to 3.2 mg. per 100 cc. and the diagnosis was made on the basis of negative calcium balance studies and skeletal lesions. Several observers have emphasized that elevated serum cal-

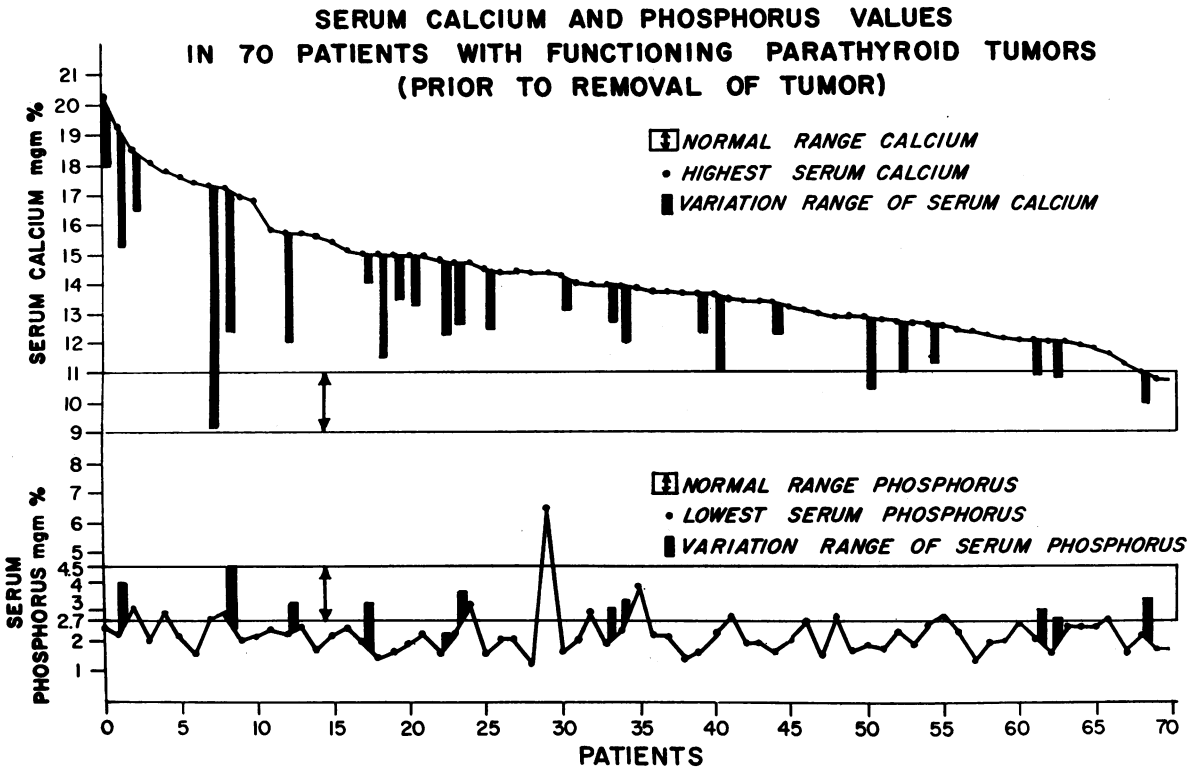

Chart 1.—The upper part of this chart lists the highest serum calcium values for the 70 individual patients with functioning parathyroid tumors and the lower part lists their lowest serum phosphorus levels. (Normal calcium content is 9 to 11 mg. per 100 cc. and normal for phosphorus 2.7 to 4.5 mg. per 100 cc.) Hypophosphatemia was not a consistent finding. Highest serum calcium levels were from 20.3 per 100 cc. down to 10.6 mg. per 100 cc. In three patients serum calcium levels never rose above 11.2 mg. per 100 cc. In five other patients serum calcium was recorded within a normal range during the time they were observed.

The solid bars indicate patients who showed a significant range of variation of chemical values and also the extent of that variation. In 25 patients the serum calcium range of variation seemed to be significant—that is, a rise or fall of greater than 1 mg. per 100 cc. In 11 of these 25 there was also a significant range of variation of the serum phosphorus, a rise or fall greater than 0.6 mg. per 100 cc.

cium is not an entirely necessary criterion for diagnosis of hyperparathyroidism.[1,2,9]

In 47 of the 70 patients with functioning parathyroid tumors, the serum calcium values showed some degree of variation. In 25 of these 47 the range of variation of serum calcium seemed to be significant—that is, beyond the accepted laboratory error for calcium (rise or fall of greater than 1 mg. per 100 cc.). Eleven of the 25 also showed a significant variation in serum phosphorus (rise or fall of more than 0.6 mg. per 100 cc.). In nine of these eleven, the serum phosphorus sometimes rose to within normal limits. Renal insufficiency, hypoproteinemia or dietary changes did not appear to be factors in these 25 cases, and all values, of course, were before excision of the parathyroid tumors. Significant ranges of variation of serum calcium and phosphorus values were encountered at as little as two-day intervals and as long as two-year intervals. Values both increased and decreased. In five patients the range of variation was from hypercalcemic levels sometimes, down to normal (9 to 11 mg. per 100 cc.) calcium levels. In one patient the serum calcium rose within a four-month period from 9.2 mg. to 17.4 mg. per 100 cc. The serum phosphorus value in this patient varied only from 2.8 mg. to 3.2 mg. per 100 cc.

These variations in the serum calcium and phosphorus values are highly suggestive of intermittent function of the parathyroid tumor. The possibility of finding a parathyroid adenoma even in the presence of normal chemical values also emphasizes the difficulty in making the diagnosis. A provocative test is needed to assure the maximum function of the tumor at the time chemical tests are being done. Also, as noted previously, a method for direct assay of the parathormone would be extremely helpful.

DISCUSSION

Although intermittent function of parathyroid tumors has been previously noted,[9,10] it has seldom been emphasized. The evidence for intermittent function of parathyroid tumors as seen in this study

can be classed as both clinical and chemical. There are several clinical indications: (1) The occurrence of both functioning and nonfunctioning adenomas and functioning and nonfunctioning carcinomas. (2) Instances of hyperparathyroid crisis or "hypercalcemic poisoning" indicate varying degrees of activities of the tumors. (3) In cases in which the patient is normal for a time after operation and then has "recurrent" adenoma, it is possible the lesion actually is a quiescent adenoma previously overlooked at the initial operation. This of course is speculative, but is another possibility for consideration in explanation of intermittent function. (4) A study of the pathologic features of parathyroid tumors done at Columbia-Presbyterian Medical Center by Kleinfeld[7] showed no correlation between the size of tumors and the duration of symptoms. With larger tumors usually the serum calcium content is higher, but at times it may be very high with small tumors also.[4] This suggests differences in growth rates and differences in tumor activity. (5) Intermittent activity is characteristic of other endocrine tumors such as pheochromocytoma and islet cell tumors of the pancreas and should certainly be also characteristic of parathyroid tumors.

This clinical evidence of intermittent function is further substantiated by the previously discussed variations in chemical values (Chart 1). Perhaps a greater appreciation of the quiescent phase of parathyroid tumors will enable us to detect more parathyroid tumors by doing repeated serum calcium and serum phosphorus determinations.

Without more direct methods of evaluating patients for hyperparathyroidism, repeated serum calcium and phosphorus determinations on three successive days or three times per week at three to four-month intervals are recommended in all patients with opaque calculus or whenever hyperparathyroidism is suspected. In view of the limitations of diagnostic tests today a more liberal attitude toward surgical exploration for parathyroid tumors is recommended to avoid the irreversible renal damage and inevitable fatal outcome if the tumor is not removed.

630 West 168th Street, New York 32, New York.

REFERENCES

1. Beard, D. E., and Goodyear, W. E.: Hyperparathyroidism and urolithiasis, J. Urol., 64:638-642, 1950.

2. Black, B. M.: Surgical aspects of hyperparathyroidism, Am. Surg., 20:1044-1050, 1954.

3. Chambers, E. L., Jr., Gordon, G. S., Goldman, L., and Reifenstein, E. C., Jr.: Tests for hyperparathyroidism: Tubular reabsorption of phosphate, phosphate deprivation and calcium infusion, J. Clin. Endocrinol., 16:1507-1521, 1956.

4. Hellstrom, J.: Primary hyperparathyroidism—observations in 50 cases, Acta Endocrinologica, 16:30-58, 1954.

5. Howard, J. E., Hopkins, T. R., and Connor, T. B.: On certain physiological responses to intravenous injection of calcium salts into normal, hyperparathyroid and hypoparathyroid persons, J. Clin. Endocrinol., 13:1-19, 1953.

6. James, P. R., and Richards, P. G.: Parathyroid crisis; treatment by emergency parathyroidectomy, A.M.A. Arch. Surg., 72:553-556, 1956.

7. Kleinfeld, G.: A clinical and pathological study of 63 functioning parathyroid tumors, Cancer, 12:902-911, 1959.

8. Kyle, L. H., Schaaf, M., and Canary, J. J.: Phosphate clearance in the diagnosis of parathyroid dysfunction, Am. J. Med., 24:240-248, 1958.

9. Richardson, J. E.: The early renal symptoms of parathyroid tumors, Ann. Royal Coll. of Surg. Eng., 13:100-126, 1953.

10. Whitby, L. G.: Intermittent hyperparathyroidism, Lancet: 1:883-885, 1958.